An official American Thoracic Society/European Respiratory Society statement: research questions in COPD

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ABSTRACT Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity, mortality and resource use worldwide. The goal of this official American Thoracic Society (ATS)/European Respiratory Society (ERS) Research Statement is to describe evidence related to diagnosis, assessment, and management; identify gaps in knowledge; and make recommendations for future research. It is not intended to provide clinical practice recommendations on COPD diagnosis and management.

Clinicians, researchers and patient advocates with expertise in COPD were invited to participate. A literature search of Medline was performed, and studies deemed relevant were selected. The search was not a systematic review of the evidence. Existing evidence was appraised and summarised, and then salient knowledge gaps were identified.

Recommendations for research that addresses important gaps in the evidence in all areas of COPD were formulated *via* discussion and consensus.

Great strides have been made in the diagnosis, assessment and management of COPD, as well as understanding its pathogenesis. Despite this, many important questions remain unanswered. This ATS/ERS research statement highlights the types of research that leading clinicians, researchers and patient advocates believe will have the greatest impact on patient-centred outcomes.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality. Given the 10-year interval since publication of the official American Thoracic Society (ATS)/European Respiratory Society (ERS) standards for the diagnosis and treatment of patients with COPD [1], leaders of the societies felt a need to summarise evidence related to the diagnosis, assessment, and management of COPD; identify knowledge gaps and research questions; and make recommendations for future research. This research statement is not intended to be a clinical practice guideline; other documents are available that provide clinical recommendations for stable COPD [2, 3], and a forthcoming ATS/ERS document will provide clinical recommendations related to COPD exacerbations.

Methods

The methods used to develop this research statement are described in the full-length version of the document, found at www.atsjournals.org and www.erj.ersjournals.com

Definitions

COPD

The ATS and ERS define COPD as a preventable and treatable disease state characterised by airflow limitation that is not fully reversible [1]. The airflow limitation is usually progressive and associated with a chronic inflammatory response of the lungs to noxious particles or gases. Cigarette smoking is the most common risk factor [4], but others are increasingly being recognised (*e.g.* biomass fuels and α_1-antitrypsin deficiency). Dyspnoea and exacerbations are the most prominent respiratory manifestations of COPD. In most patients, COPD represents the pulmonary component of a chronic multimorbidity.

Outcomes

Outcomes are the results of an intervention. Traditionally, many outcomes measured in COPD research have been physiological, such as lung function (*e.g.* forced expiratory volume in 1 s (FEV_1)) or functional capacity (*e.g.* 6-min walking distance). Physiological outcomes are desirable because they are readily measured, provide information about disease progression, and are related to clinical outcomes such as mortality and exacerbations. Anatomical outcomes have also been used in studies of COPD, such as histological or imaging findings. Physiological and anatomical outcomes make research easier, more efficient and less costly.

There is increasing recognition, however, that the relationship between many surrogate outcomes (*i.e.* physiological and/or anatomical outcomes) and outcomes that matter to patients (*i.e.* "patient-centred" or "patient-important" outcomes, such as dyspnoea, quality of life, frequency of exacerbations, frequency of hospitalisations and mortality) is modest at best, and interventions that improve surrogate outcomes frequently do not affect patient-centred outcomes. As a result, there is increasing emphasis on: 1) using patient-centred outcomes in clinical research; and 2) finding high-quality surrogate outcomes that reliably predict patient-centred outcomes [5].

We recommend:

- Studies that determine which outcomes matter most to patients with COPD and, therefore, are truly patient-centred outcomes in this population.
- Studies that correlate physiological and anatomical outcomes with patient-centred outcomes, to identify high-quality surrogate outcomes that may be used in future research.
- Preferential use of patient-centred outcomes to inform judgments related to patient care until surrogate outcomes have been identified that strongly correlate with patient-centred outcomes.

Clinical manifestations and initial assessment

The diagnosis of COPD is first suspected when a patient: 1) complains of a cough, sputum production, dyspnoea, or recurrent lower respiratory infections; 2) reports risk factors for the disease, such as exposure to cigarette smoke or environmental or occupational pollutants; or 3) presents with an acute exacerbation. The physical examination is performed to identify respiratory and systemic effects of COPD. A normal

physical examination is common in mild COPD, with signs (*e.g.* quiet breath sounds, a prolonged expiratory duration and weight loss) becoming apparent as the disease progresses.

Chest radiography is generally performed during the initial diagnostic evaluation of patients with suspected COPD to exclude other diseases that may cause similar symptoms and signs and to establish the presence of concomitant respiratory diseases. It is frequently normal in early COPD. Computed tomography (CT) can estimate the degree of emphysema and its distribution and identify bronchial wall thickening and gas trapping. These estimates correlate with lung function abnormalities, but there are substantial variations among those interpreting the studies [6, 7]. To mitigate interpreter variability, numerous quantitative techniques have been applied [8, 9]. For many reasons, however, these techniques have not become routine clinical practice [10–13].

Additional advantages of CT scanning are that it can help differentiate between structural abnormalities that cause airflow limitation (*e.g.* emphysema, bronchiolitis and bronchiectasis), identify abnormalities that are associated with clinically significant features (*i.e.* phenotypes), and detect both pulmonary comorbidities (*e.g.* lung cancer, interstitial lung disease and pulmonary hypertension) and nonpulmonary comorbidities (*e.g.* coronary artery calcifications, heart failure and diseases of the mediastinum) [14].

We recommend:

- Studies to determine whether there is a role for routine CT scanning among patients with newly diagnosed COPD.
- Studies to identify CT findings that reliably and consistently correlate airway dimension measurements with lung function, using pulmonary function tests as the reference standard.
- Studies to identify CT findings that are associated with clinically significant features (*i.e.* phenotypes) and differential responses to treatment.
- Studies to determine the optimal CT protocol and quantification methods. The results may allow CT scans performed using different types of CT scanners to be compared with one another, which would facilitate longitudinal assessment, multicentre trials, and multicentre clinical care.

Diagnosis

Diagnosis of COPD requires confirmation of an airflow limitation that is not fully reversible *via* spirometry in a patient who has a history of a potentially causative exposure (*e.g.* smoking). Airflow limitation that is not fully reversible is defined by a low post-bronchodilator FEV_1/forced vital capacity (FVC) ratio [1].

The threshold FEV_1/FVC ratio that should be used to confirm an airflow limitation is uncertain. A post-bronchodilator FEV_1/FVC ratio of <0.7 has traditionally been the criterion for airflow limitation [1]. However, this threshold may result in more frequent identification of airflow limitation and, hence, more frequent diagnosis of COPD among the elderly [15] and less frequent diagnosis among young adults <45 years of age [16] compared with a threshold based on the lower limit of normal (LLN) of FEV_1/FVC. Advocates for the fixed ratio argue that it identifies a number of patients with significant pulmonary pathology and respiratory morbidity not detected by the LLN [17], and advocates for the LLN argue that the fixed ratio is more likely to yield false-positive results [15].

Screening asymptomatic individuals for COPD using spirometry is controversial. There is evidence that screening detects undiagnosed COPD [18]. However, asymptomatic individuals with mild airflow limitation (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 1) may not have faster lung function decline or a lower quality of life than asymptomatic individuals with normal lung function [19], and there are no data showing that outcomes improve among individuals who are identified as having COPD before developing symptoms, that early treatment provides any benefit in asymptomatic individuals, or that screening is cost effective [20].

We recommend:

- Studies that measure the accuracy of various tools (*e.g.* questionnaires) to detect symptoms in patients at risk for COPD, using spirometry as the reference standard.
- Studies that compare outcomes among individuals diagnosed with COPD on the basis of an FEV_1/FVC ratio <0.70 with those among individuals diagnosed with COPD on the basis of an FEV_1/FVC below the LLN.
- Studies that compare outcomes among symptomatic individuals whose COPD diagnosis is based on the combination of an airflow limitation confirmed by spirometry and a history of exposure to the causative agent with those among symptomatic individuals whose COPD diagnosis has not been confirmed with spirometry but rather is based on an alternative approach. Examples of alternative approaches include various combinations of symptoms, imaging findings, and physiological abnormalities measured by complementary tests such as forced oscillation techniques.

- Studies that evaluate case-finding strategies using questionnaires, mini-spirometers and office spirometry in areas where access to conventional spirometry requires specialised assessment.
- Studies that examine the impact of ascertainment (*e.g.* by spirometric screening *versus* spirometry performed due to symptoms and an exposure history) on medium- and long-term outcomes in individuals with COPD.
- Studies that evaluate the impact of age on the importance of identifying an airflow limitation (*i.e.* is it more important to identify asymptomatic airflow limitation in a 30 year old than an 80 year old?).

Assessment after diagnosis

Disease severity

The severity of a disease relates to the extent of functional impairment of the target organ(s). Classification of COPD severity by spirometry alone (table 1) predicts patient-centred outcomes, such as health status [21], use of healthcare resources [22], frequency of exacerbations [23, 24], and mortality [25]. Body mass index (BMI) and functional dyspnoea (*i.e.* dyspnoea that affects functional ability, employment, quality of life or health status [26] also predict patient-centred outcomes. BMI is obtained by dividing the weight (in kg) by the height (in m^2); values <21 $kg \cdot m^{-2}$ are associated with increased mortality [27, 28]. The severity of functional dyspnoea can be assessed using the modified Medical Research Council (mMRC) dyspnoea score (table 2) [29]. Increased functional dyspnoea is associated with increased mortality [30].

Several composite indices of disease severity have been developed (table 3) [31–37]. Although the prognostic accuracy of each of these indices has been confirmed in separate studies, few studies have directly compared one index to another.

The GOLD Global Strategy for the Diagnosis, Management, and Prevention of COPD [2] proposed a multidimensional assessment of COPD for the purposes of treatment selection. The assessment includes: 1) high/low symptoms using the mMRC dyspnoea scores, the COPD Assessment Test or the clinical COPD questionnaire; 2) the severity of airflow limitation; and 3) the number of yearly exacerbations. Patients with high symptoms (mMRC dyspnoea score ⩾2, COPD Assessment Test score ⩾10 or clinical COPD questionnaire ⩾1) and GOLD grade 3 or 4 spirometry and/or frequent exacerbations (two or more exacerbations in the preceding year and/or one hospitalisation) are considered at high risk for further exacerbations and, indirectly, poor clinical outcomes.

Concomitant chronic diseases may greatly contribute to the severity of disease in patients with COPD, and inclusion of comorbidities in the multidimensional evaluation of patients with COPD is useful in the context of comprehensively evaluating patients with COPD [38, 39].

TABLE 1 Spirometric classification of chronic obstructive pulmonary disease (COPD)

Severity of obstruction	Post-bronchodilator FEV_1/FVC	FEV_1 % predicted
At risk	>0.7	⩾80
Mild COPD	⩽0.7	⩾80
Moderate COPD	⩽0.7	50–80
Severe COPD	⩽0.7	30–50
Very severe COPD	⩽0.7	<30

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. At risk are patients who: smoke or have exposure to pollutants; have cough, sputum or dyspnoea; and have a family history of chronic respiratory disease.

TABLE 2 Modified Medical Research Council Dyspnoea Scale

Grade	Description
0	Not troubled with breathlessness, except during strenuous exercise
1	Troubled by shortness of breath when hurrying or walking up a slight hill
2	Walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on a level surface
3	Stops for breath after walking about 100 m or after a few minutes on a level surface
4	Too breathless to leave the house or breathless when dressing or undressing

TABLE 3 Composite prognostic indexes in chronic obstructive pulmonary disease

Composite index	Components	[Ref.]
BODE	BMI, FEV_1, mMRC dyspnoea scale and 6MWD	[31]
mBODE	BMI, FEV_1, mMRC dyspnoea scale and $V'O_{2peak}$	[32]
eBODE	BMI, FEV_1, mMRC dyspnoea scale, 6MWD and exacerbation rate	[33]
BODEx	BMI, FEV_1, mMRC dyspnoea scale and exacerbation rate	[34]
Inflammatory BODE	BODE, inflammatory biomarkers, age and hospitalisation history	[35]
ADO	Age, mMRC dyspnoea scale and FEV_1	[36]
DOSE	mMRC dyspnoea scale, FEV_1, smoking status and exacerbation rate	[37]
CODEx	Comorbidity, obstruction, dyspnoea and previous severe exacerbations	[39]

BODE: body mass index (BMI), airflow obstruction, dyspnoea, exercise capacity; mBODE: modified BODE in which 6MWD is replaced by peak oxygen consumption; eBODE: exacerbations added to the original BODE; BODEx: exacerbations replace 6MWD in the original BODE; inflammatory BODE: inflammatory markers added to the original BODE; ADO: age, dyspnoea and airflow obstruction index; DOSE: dyspnoea, airflow obstruction, smoking status and exacerbations index; CODEx: comorbidities, airflow obstruction, dyspnoea and exacerbations index;. FEV_1: forced expiratory volume in 1 s (severity of airflow obstruction); mMRC: modified Medical Research Council; 6MWD: 6-min walking distance; $V'O_{2peak}$: peak oxygen consumption.

We recommend:

- Studies that determine which index or indices best stratify patients for the purpose of determining disease severity or recommending treatment.
- Studies that determine if short-term changes in these indices or other measures (*e.g.* lung function, CT findings and biomarkers) are useful surrogate markers of medium- or long-term patient-centred outcomes, thus shortening the time needed to complete therapeutic trials.
- Studies that contribute to a better understanding of the pathogenesis, impact, prevention and treatment of concomitant diseases in patients with COPD.

Disease activity

Activity of a disease relates to the level of activation of the biological processes that drive disease progression. The biological processes that drive disease progression in COPD are likely to be related to the balance between the pulmonary and systemic inflammatory responses to inhalational injury and the subsequent repair process [40]. In theory, identifying and treating active pathological processes may mitigate or eliminate disease progression.

It is unclear how to measure disease activity. Potential surrogate markers include the rate of change of clinical markers of disease progression, because faster rates of disease progression presumably indicate more disease activity. Examples of clinical markers of disease progression include worsening dyspnoea and health status, loss of exercise capacity, cough and sputum production, active smoking, appearance or worsening of comorbidities, weight loss and frequency of exacerbations [41, 42]. Other measures can be categorised as functional markers (*e.g.* FEV_1 decline, deterioration of the diffusing capacity of the lung for carbon monoxide and progressive hyperinflation), structural markers (*e.g.* progression of emphysema, worsening of airway dimensions and appearance or worsening of bronchiectasis), and biological markers (*e.g.* biological markers in the lung, circulating blood, exhaled air and/or urine).

We recommend:

- Studies that relate potential biomarkers of disease activity (*e.g.* rate of lung function decline, increased exacerbation frequency, inflammation, lung tissue destruction and repair responses induced by inhalational injury) to patient-centred outcomes to validate the biomarkers as clinically useful measures of disease activity.
- Studies that evaluate the impact of disease activity on treatment response and, conversely, the effects of treatment on disease activity.

Phenotyping

A phenotype is the observable properties of an organism, which are determined by its genotype and modulated by its environment [43]. A clinical COPD phenotype has been defined as "A single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (*e.g.* symptoms, exacerbations, response to therapy, rate of disease progression or death)" [44].

Clinical phenotyping may be complicated for several reasons. First, the presentation of some clinical phenotypes may change due to either the effect of therapy and/or the natural course of the disease.

Secondly, although a COPD phenotype describes differences between individuals with COPD, a given patient can have more than one clinical phenotype. Finally, two prevalent diseases can coexist (*e.g.* COPD and obstructive sleep apnoea, or COPD and asthma).

Only a few COPD phenotypes have been validated. They include α_1-antitrypsin deficiency, frequent (two or more per year) exacerbations, chronic bronchitis and upper lobe emphysema with poor exercise tolerance after rehabilitation in patients with severe airflow limitation. Other COPD phenotypes have been proposed but still require validation confirming their relationship with clinically meaningful outcomes: severe hypoxaemia, disproportionate symptoms, persistent systemic inflammation, chronic airway bacterial colonisation, emphysema predominance with pulmonary hyperinflation and lung cancer, the asthma/COPD overlap syndrome, premature or early severe airflow limitation (<55 years), out-of-proportion pulmonary hypertension (mean pulmonary arterial pressure >40 mmHg), COPD in never-smokers, and the four new patient types (*i.e.* types A, B, C and D) proposed by GOLD [2]. Even if some of these phenotypes are associated with clinically meaningful outcomes, many experts believe that research should focus on those phenotypes where outcomes can be modified with therapy. In fact, exploratory therapeutic interventions in targeted populations are recommended for the validation of a clinical phenotype.

We recommend:

- Studies to relate potential phenotypic traits with outcomes. Such evidence may provide more individualised prognostic information.
- Studies to relate potential phenotypic traits with response to therapy. Such evidence may identify specific types of patients who are more or less likely to respond to a given therapy, facilitate the development of personalised medicine, and increase the priority of future research studies that plan to enrol phenotypes whose outcomes can be potentially modified by therapy.
- Studies to enhance understanding of the treatment impact of various COPD phenotypes (*e.g.* asthma/COPD overlap, α_1-antitrypsin deficiency, bronchiectasis, *etc.*).

Comorbidities

COPD is frequently associated with one or more comorbidities and/or systemic effects. Therefore, in many patients it can be considered just the pulmonary component of the multimorbidity that is characterised by concomitant chronic diseases (*e.g.* hypertension, atherosclerosis, chronic heart failure, lung cancer, osteoporosis, depression, *etc.*) and systemic effects (*e.g.* weight loss and muscle weakness) that are not fully explained by ageing and other common risk factors (*e.g.* smoking, diet, inactivity, lifestyle, *etc.*) [45–47]. Chronic comorbidities are prominent contributors to the clinical severity of patients with COPD, as they often affect important patient-centred outcomes.

Ischaemic heart disease is a common comorbidity, contributing to worsening health and functional status [48], increased risk of a longer exacerbation [48], more dyspnoea [48], and decreased survival [49]. COPD is also associated with an increased incidence of lung cancer [50, 51] and prevalence of diabetes, hypertension and other cardiovascular diseases, even after controlling for tobacco smoking in some studies. Evidence supports the clustering of certain comorbidities with COPD [52], thereby suggesting potential common pathobiological pathways for these diseases. There is also increasing evidence that acute exacerbations of respiratory symptoms in patients with COPD may be caused by extrapulmonary mechanisms and exacerbations of concomitant chronic diseases, such as systemic arterial hypertension, acute heart decompensation, atrial fibrillation and pulmonary embolism [53]. Conversely, COPD exacerbations appear to impact the risk of cardiovascular events [54]. Although acute exacerbations of respiratory symptoms occur more frequently in patients with COPD, they also occur with significant frequency in smokers without COPD, suggesting that they are not specific for COPD [54, 55]. Patients with COPD have a similar prevalence of sleep apnoea as the general population. When this overlap syndrome exists, patients are treated with continuous positive airway pressure, because this has been shown to decrease mortality [56].

We recommend:

- Studies to confirm or exclude an association between specific comorbidities and COPD.
- Studies to elucidate pathobiological mechanisms linking COPD to its comorbidities.
- Studies to explore the mechanisms of exacerbations of respiratory symptoms in patients with COPD.
- Studies to determine the nature and optimal therapeutic management of patients with concomitant chronic diseases, particularly heart failure and/or ischaemic heart disease.

Pathophysiology and pathology

The pathophysiology and pathology of COPD are described in the full-length version of the document, found at www.atsjournals.org and www.erj.ersjournals.com

Management

Smoking cessation

Stopping smoking increases life expectancy at any age [57]. Smoking cessation reduces the rate of decline of lung function in patients with COPD and, therefore, is an important goal of treating smokers with COPD [58]. It has been hypothesised that objective evidence of disease may motivate smokers to quit. This was supported by a study that found that communicating the results of spirometry in terms of the smoker's "lung age" (*i.e.* the age at which a healthy individual acquires similar results) improved the likelihood of smoking cessation [59]. However, other data are conflicting. Two studies found that smokers whose spirometry identified COPD had higher quit rates than smokers whose spirometry did not identify COPD [60, 61], whereas another study found that confronting smokers with abnormal spirometry results did not improve smoking cessation rates [62].

Smokers with COPD appear to be just as responsive as smokers without COPD to pharmacotherapy directed at smoking cessation. This is supported by the observation that smoking quit rates were similar in trials that enrolled smokers with mild-to-moderate COPD compared with trials that enrolled general populations of smokers [63–66]. It is unknown whether these findings apply to patients with severe COPD because such patients have been scarcely studied. It is likely that some comorbidities affect responsiveness to smoking cessation interventions and others do not. For example, studies have shown that depression negatively impacts smoking cessation [67], whereas cardiovascular disease does not [68].

Pharmacological aids for smoking cessation can be allocated into two categories: controllers (*e.g.* nicotine patch, bupropion and varenicline), which target long-term abstinence; and relievers (*e.g.* nicotine gum) for rapid relief of acute cravings for tobacco or heightened withdrawal symptoms. Generally speaking, the controller medication is taken on a regular dosing schedule, with the dose and duration determined by the severity of nicotine dependence and symptoms of withdrawal. The reliever is used on an as-needed basis to manage acute urges to smoke or breakthrough withdrawal symptoms. Although this strategy is intuitive and has been anecdotally successful, its outcomes have not been studied in controlled trials.

Pharmacotherapy plus counselling improves smoking cessation compared with either pharmacotherapy or counselling alone [69, 70]. However, the optimal intensity of counselling is unknown [66, 71].

Electronic cigarettes (*i.e.* e-cigarettes) are battery-powered devices that, when puffed like a cigarette, produce vapours that can contain nicotine. This eliminates the inhalation of most of the toxic constituents of tobacco cigarettes, although the risks of e-cigarettes are incompletely understood. E-cigarettes are growing in popularity because they have behavioural features similar to those of conventional cigarettes, yet are presumed to be a less harmful alternative that can decrease both cravings and withdrawal symptoms. They are being used as either a substitute for conventional cigarettes or as an aid to quitting smoking [72–74]. Additional research on e-cigarettes has become an urgent need because the presumed benefits of e-cigarettes are unproven and the long-term risks are unknown, yet e-cigarettes are commercially available and becoming increasingly popular [75]. In particular, the efficacy of e-cigarettes as a smoking cessation strategy is unknown. A concern is that individuals who might otherwise avoid regular cigarette smoking due to fear of adverse health effects might be attracted to presumably safer electronic cigarettes and thereby become addicted to nicotine. The Forum of International Respiratory Societies, which includes the ATS and ERS, has published a position statement on e-cigarettes [76].

Patients frequently fail to quit smoking and, therefore, ask whether decreased smoking is sufficient to derive some benefit. Although one study suggests that smoking reduction improves respiratory symptoms [77], it is unclear if smoking reduction slows the rate of lung function decline [78–81]. Studies suggest that smoking reduction is associated with a greater probability of future cessation [81]

Marijuana smoking is now legal in two states within the USA for recreational purposes and for medical purposes in several others, yet the risk of marijuana smoking on the development of COPD is uncertain. As an example, multiple studies have found that long-term marijuana smoking is associated with symptoms of COPD, but an association with fixed airflow obstruction has been inconsistent [82]. The reasons for the inconsistent findings are not understood.

We recommend:

- Studies comparing the smoking quit rate of individuals who undergo spirometry with the smoking quit rate of those who do not undergo spirometry, using different techniques to add value to the spirometry results (*e.g.* lung age and functional limitation). Among those undergoing spirometry, quit rates should be compared among those with and without airflow obstruction.
- Studies to clarify the optimal approach to achieve abstinence from smoking. Examples include a controller plus a reliever *versus* a controller or reliever alone, various combinations and durations of pharmacological agents, various intensities of counselling, and add-on therapies if initial therapy fails.

- Studies that measure the potential benefits (*i.e.* smoking quit rate, incidence of COPD and incidence of lung cancer) and harms (*i.e.* addiction rate, toxicology, carcinogenesis and cost-effectiveness) of e-cigarettes, both short- and long-term.
- Studies that compare outcomes among patients who have quit smoking, reduced the amount that they smoke, or continued smoking the same amount.
- Studies investigating the genetic basis of smoking addiction and cessation.
- Studies comparing existing smoking cessation strategies and seeking novel smoking cessation strategies and drugs.
- Studies to determine whether marijuana smoking increases the incidence of COPD and, if so, to identify which individuals are at greatest risk.

Standard pharmacological therapies

Lung function is improved and the frequency of acute COPD exacerbations is reduced by long-acting β-agonists (LABAs), inhaled corticosteroids (ICS), combined LABA/ICS, and long-acting antimuscarinic antagonists (LAMAs) [83–85]. Health-related quality of life is also improved by ICS, LABAs, LABA/ICS and LAMAs [83–85]. LABA/ICS and LAMAs may improve mortality in unselected patients with COPD [83, 84], although the evidence for this effect is limited because the studies had a low event rate due to the inclusion of patients at low risk for mortality [86]. Finally, the rate of decline of lung function might be reduced by inhaled medications, but this is only supported by subgroup analyses [87, 88] of randomised trials [83, 84]. All of these effects are modest, possibly due to differential effects on COPD subtypes.

An as-needed inhaled short-acting β-agonist is generally the first medication initiated, often with a standing dose of an inhaled long-acting bronchodilator. However, the optimal long-acting bronchodilator regimen is unknown. In a systematic review of seven randomised trials that directly compared a LAMA (*i.e.* tiotropium) with LABAs, meta-analyses found that the LAMA had a greater effect on reducing COPD exacerbations, exacerbation-related hospitalisations and adverse effects, but there were no differences in mortality, all-cause hospitalisations, symptoms or lung function [89]. The meta-analyses were limited by heterogeneity, suggesting that the differences between the LAMA and LABAs may have been due to the specific LABA (*i.e.* salmeterol, formoterol or indacaterol), the population studied or genetic predisposition [90]. In other words, whereas the LAMA was superior to the LABAs collectively, the possibility that one of the LABAs is superior to the LAMA in some subgroups or the entire COPD population cannot be excluded. The meta-analyses evaluated only the 12-h LABAs because they preceded the introduction of 24-h acting LABAs; however, a subsequent direct comparison between the LAMA tiotropium and the 24-h LABA indacaterol confirmed the superiority of LAMAs in reducing exacerbations [91].

The LABA/ICS combination is sometimes added instead of an inhaled long-acting bronchodilator. The combination improves health-related quality of life and reduces the risk of a moderate or severe COPD exacerbation when compared with placebo, LABA alone or ICS alone [83]. The combination also reduces the rate of lung function decline when compared with placebo but not when compared with a LABA alone or ICS alone [83]. The LABA/ICS combination may have a modest effect on overall mortality [83]. The primary adverse effect attributed to the LABA/ICS combination is an increased risk of pneumonia, although this effect may not be present to the same degree with all formulations of a LABA/ICS [92, 93].

The LABA/ICS combination was equivalent to the LAMA in terms of exacerbation prevention in the only direct comparison with a LAMA [94]. Several other outcomes (*i.e.* health status and mortality) favoured the LABA/ICS combination over the LAMA, but confidence in these results is limited by the small number of events [94]. Adding a LAMA to the LABA/ICS combination appears to reduce the rate of severe exacerbations and improve symptoms in patients with moderate or severe COPD [95].

LABA/LAMA combinations have been developed and appear to increase lung function to a greater degree than a LAMA alone [96]. The effect of the LABA/LAMA combination on the frequency of COPD exacerbations is less certain because it reduced the frequency when compared with one LAMA (*i.e.* glycopyrrolate) but not when compared with another LAMA (*i.e.* tiotropium) [96]. More studies are needed to determine the effect of the LABA/LAMA combination on other patient-centred outcomes.

Few studies have investigated the indications and benefits of adding medications or the safety of withdrawing medications, although one trial suggested that withdrawal of inhaled corticosteroids may not increase the risk of moderate or severe COPD exacerbations [97]. Similarly, causes, effects and management of nonadherence and misuse of inhalers have been scarcely studied.

We recommend:

- Therapeutic trials that analyse outcomes among different COPD subtypes, particularly those subtypes that are at greatest risk for an undesirable outcome.

- Therapeutic trials that compare outcomes among current smokers with former smokers.
- Therapeutic trials that evaluate outcomes using different thresholds for initiating, adding and withdrawing medications.
- Therapeutic trials that compare outcomes among patients treated with different medications (as opposed to placebo-controlled studies). Examples include: 1) comparisons of LAMA therapy with each type of LABA therapy (*i.e.* salmeterol, formoterol, indacaterol, olodaterol and vilanterol); and 2) comparisons of combination LAMA/LABA therapy with LABA/ICS, LAMA and LABA therapy.
- Trials comparing strategies of pharmacological treatment (*e.g.* treatment initiation with one single agent and then further step-up if symptoms are not controlled *versus* immediate double or triple therapy).
- Studies of therapies aimed at improving cough, sputum production and dyspnoea, all of which are of importance to patients.
- Studies assessing how pharmacological treatment complements rehabilitation programmes.
- Real-life observational studies (*i.e.* effectiveness studies) that assess how the results of randomised trials (*i.e.* efficacy trials) may be applied to broader patient populations in usual care settings.
- Studies that determine the risk for pneumonia conferred by each formulation of the LABA/ICS combination, as well as the aetiology and natural history of pneumonia in ICS-treated patients.
- Studies that evaluate the effects of treating common comorbidities on COPD-specific outcomes, as well as the effects of treating COPD on outcomes specific to common comorbidities.
- Studies that identify and validate instruments that objectively determine a patient's response to therapy.
- Studies that compare outcomes among patients managed with various strategies to improve adherence.
- Studies that compare outcomes among patients who use an inhaler with those who use a nebuliser.
- Studies of patients who are diagnosed with COPD at an early age to determine if early intervention reduces disease progression.

Novel pharmacological therapies

Novel pharmacological therapies (*i.e.* anti-inflammatory therapies, long-term antibiotic therapy and statin therapy) are discussed in the full-length version of the document, found at www.atsjournals.org and www.erj.ersjournals.com

Managing comorbidities

Management of the rising prevalence of multiple chronic comorbidities (*i.e.* patients with two or more chronic comorbidities) is a major challenge facing healthcare systems worldwide, which are dominated by single-disease approaches [98]. In many patients, COPD should be considered to be just one component of multiple chronic comorbidities. Generally speaking, patients with COPD and multiple chronic comorbidities are treated according to existing standards for each individual disease. In other words, comorbidities in patients with COPD are treated the same as in patients without COPD, and COPD is treated the same regardless of the comorbidity. Observational studies suggest that mortality of patients with COPD can be reduced by nonrespiratory treatments, including β-blockers, angiotensin-converting enzyme inhibitors [99] and statins [100].

We recommend:

- Studies that evaluate the effects of treating COPD on the outcomes of comorbid diseases, as well as studies that evaluate the effect of treating comorbid diseases on COPD-related outcomes.

Nonpharmacological therapies

Pulmonary rehabilitation

Pulmonary rehabilitation is typically provided in a hospital-based outpatient setting. Its benefits in this setting are well established, including reduced dyspnoea, increased exercise capacity, improved quality of life and reduced use of healthcare resources [101]. Effects on physical activity are less well studied and less consistent. More recent research has focused on the effectiveness of pulmonary rehabilitation in alternative settings.

Home-based pulmonary rehabilitation might improve patient-centred outcomes in a manner comparable to hospital-based programmes, including health-related quality of life and exercise capacity [102]. A randomised trial compared cycle ergometer exercise training in the home with the same training in a pulmonary rehabilitation centre [103]. Dyspnoea and exercise tolerance improved to an equivalent degree in both groups, and there were no significant safety issues in either group. However, critics have argued that the magnitude of benefit in the hospital-based pulmonary rehabilitation group was smaller than usual, potentially biasing the results towards no difference. This highlights the need for confirmatory studies before concluding that home-based pulmonary rehabilitation programmes provide outcomes similar to hospital-based programmes.

Community-based pulmonary rehabilitation has been compared with no pulmonary rehabilitation in a 2-year randomised trial, which found that community-based pulmonary rehabilitation improved dyspnoea, exercise endurance, strength and nutritional indices [104, 105]. The total cost of the intervention was higher than usual care at 4 months, but this was offset at 24 months due to reduced hospital admission costs.

Pulmonary rehabilitation programmes are effective in patients after (severe) exacerbations. A systematic review identified improvement in symptoms, health-related quality of life and exercise tolerance, as well as possible benefits in hospital readmission rates and survival [106].

Pulmonary rehabilitation and pharmacotherapy appear to be complementary approaches to COPD care with synergistic effects [107]. Additional details about the evidence for pulmonary rehabilitation in patients with COPD are provided in an ATS/ERS statement on pulmonary rehabilitation [101].

We recommend:

- Studies that compare the effects of home-based pulmonary rehabilitation with hospital-based pulmonary rehabilitation.
- Studies that compare hospital-based, home-based and community-based pulmonary rehabilitation in different subtypes of patients with COPD, to determine which settings are most appropriate for the various types of patients.
- Long-term studies that compare the effects of hospital-based, home-based and community-based pulmonary rehabilitation on the maintenance of benefits. Of particular importance is evaluation of the effects of such programmes on physical activity.
- Studies that compare the effects of various modalities, supervision protocols and programme durations on outcomes.
- Controlled trials of early intensive rehabilitation in patients recovering from exacerbations to evaluate its potential effect on readmission rates and other outcomes.
- Studies that evaluate strategies to maintain the benefits of pulmonary rehabilitation.

Long-term oxygen therapy

Long-term oxygen therapy (LTOT) reverses hypoxaemia. A trial that compared LTOT with no oxygen therapy in patients with COPD with severe hypoxaemia (arterial oxygen tension (*P*aO2) $\leqslant$55 mmHg) found that LTOT improved survival [108], whereas another trial that compared oxygen administered for 19 h·day^{-1} with oxygen administered for 12 h·day^{-1} found that the longer duration improved survival [109]. In contrast, a trial that compared LTOT with no oxygen therapy in patients with COPD with moderate hypoxaemia (*P*aO2<69 mmHg) found no effect on survival, regardless of the duration used per day [110]. This evidence has limitations: the trials included relatively few patients and events (only 370 patients and 164 deaths, collectively), there was a paucity of women enrolled, and two of the three trials were conducted more than 30 years ago.

These data suggest that LTOT has a mortality benefit that may be related to the severity of hypoxaemia. Thus, LTOT is routinely prescribed for patients with severe hypoxaemia. The National Institutes of Health has funded a trial comparing supplemental oxygen with no supplemental oxygen among patients with mild-to-moderate hypoxaemia, the Long-term Oxygen Treatment Trial (LOTT). Among patients in the supplemental oxygen group, those with hypoxaemia at rest will be instructed to use the supplemental oxygen continuously, whereas those with hypoxaemia during exertion will be instructed to use the supplemental oxygen with exertion and during sleep only.

We recommend:

- Studies that measure the effects of LTOT on outcomes in various COPD subtypes. Examples of subtypes that warrant evaluation include patients with mild and moderate hypoxaemia, desaturation with exertion, desaturation during sleep, comorbid heart disease, frequent exacerbations, decreased exercise capacity or pulmonary hypertension.
- Studies that evaluate the effect of LTOT on physical activity and the relationship of this effect on other outcomes, such as quality of life, frequency of exacerbations, and mortality.
- Studies that compare the effects of various modalities of LTOT (*e.g.* continuous, exercise, sleep, combined, with or without flow titration) on outcomes in different patient subtypes.

Noninvasive mechanical ventilation

Noninvasive mechanical ventilation (NIV) improves respiratory acidosis and decreases respiratory rate, severity of breathlessness, intubation rate, length of hospital stay and mortality in patients with COPD who are experiencing acute on chronic respiratory failure [111–115]. Despite the success of NIV for acute respiratory failure, the effects of long-term NIV in patients with COPD who have chronic respiratory failure remain controversial [116, 117]. Some studies have shown benefits in health status, dyspnoea or blood gases, but there has been little or no impact on other outcomes such as rehospitalisation rates or mortality [118–120]. An exception is a recent study that found that NIV may improve survival in patients

with COPD with chronic respiratory failure [121]. Uncertainty about the effects of NIV in patients with COPD with chronic respiratory failure has led to the use of NIV on an individual basis.

We recommend:

- Studies that assess the effects of long-term NIV in patients with COPD who have chronic respiratory failure.
- Studies that identify characteristics of patients who are most likely to benefit from long-term NIV.

Lung volume reduction surgery, lung transplantation and nutrition

Lung volume reduction surgery, lung transplantation and nutrition are discussed in the full-length version of the document, found at www.atsjournals.org and www.erj.ersjournals.com

Integrative management, end-of-life care, pre-operative evaluation and air travel risk assessments

Integrative management, end-of-life care, pre-operative evaluation and air travel risk assessments are discussed in the full-length version of the document, found at www.atsjournals.org and www.erj.ersjournals.com

Conclusion

COPD is a leading cause of morbidity, mortality and resource use. Strides have been made in the identification, pathogenesis, assessment and treatment of COPD, yet many important questions remain unanswered. This ATS/ERS research statement highlights the types of research that leading clinicians and researchers believe will have the greatest impact on patient-centred outcomes.

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References

1 Celli BR, MacNee W, Agusti A, *et al.* Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.

2 Vestbo J, Hurd SS, Agustí AG, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013; 187: 347–365.

3 O'Reilly J, Jones MM, Parnham J, *et al.* Management of stable chronic obstructive pulmonary disease in primary and secondary care: summary of updated NICE guidance. *BMJ* 2010; 340: c3134.

4 Rostron BL, Chang CM, Pechacek TF. Estimation of cigarette smoking-attributable morbidity in the United States. *JAMA Intern Med* 2014; 174: 1922–1928.

5 Jones P, Miravitlles M, van der Molen T, *et al.* Beyond FEV1 in COPD: a review of patient-reported outcomes and their measurement. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 697–709.

6 Oga T, Nishimura K, Tsukino M, *et al.* Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003; 167: 544–549.

7 Coxson HO, Lam S. Quantitative assessment of the airway wall using computed tomography and optical coherence tomography. *Proc Am Thorac Soc* 2009; 6: 439–443.

8 Copley SJ, Wells AU, Müller NL, *et al.* Thin-section CT in obstructive pulmonary disease: discriminatory value. *Radiology* 2002; 223: 812–819.

9 Coxson HO, Mayo J, Lam S, *et al.* New and current clinical imaging techniques to study chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009; 180: 588–597.

10 Barr RG, Berkowitz EA, Bigazzi F, *et al.* A combined pulmonary-radiology workshop for visual evaluation of COPD: study design, chest CT findings and concordance with quantitative evaluation. *COPD* 2012; 9: 151–159.

11 Galbán CJ, Han MK, Boes JL, *et al.* Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med* 2012; 18: 1711–1715.

12 Christe A, Charimo-Torrente J, Roychoudhury K, *et al.* Accuracy of low-dose computed tomography (CT) for detecting and characterizing the most common CT-patterns of pulmonary disease. *Eur J Radiol* 2013; 82: e142–e150.

13 Castaldi PJ, San José Estépar R, Mendoza CS, *et al.* Distinct quantitative computed tomography emphysema patterns are associated with physiology and function in smokers. *Am J Respir Crit Care Med* 2013; 188: 1083–1090.

14 Coxson HO, Leipsic J, Parraga G, *et al.* Using pulmonary imaging to move COPD beyond FEV1. *Am J Respir Crit Care Med* 2014; 190: 135–144.

15 Hardie JA, Buist AS, Vollmer WM, *et al.* Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002; 20: 1117–1122.

16 Cerveri I, Corsico AG, Accordini S, *et al.* Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax* 2008; 63: 1040–1045.

17 Bhatt SP, Sieren JC, Dransfield MT, *et al.* Comparison of spirometric thresholds in diagnosing smoking-related airflow obstruction. *Thorax* 2014; 69: 409–414.
18 Carlsson AC, Wändell P, Ösby U, *et al.* High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden – a challenge for public health. *BMC Public Health* 2013; 13: 670–678.
19 Bridevaux PO, Gerbase MW, Probst-Hensch NM, *et al.* Long-term decline in lung function, utilisation of care and quality of life in modified GOLD stage 1 COPD. *Thorax* 2008; 63: 768–774.
20 U.S. Preventive Services Task Force. Screening for chronic obstructive pulmonary disease using spirometry: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008; 148: 529–534.
21 Ferrer M, Alonso J, Morera J, *et al.* Chronic obstructive pulmonary disease stage and health-related quality of life. The Quality of Life of Chronic Obstructive Pulmonary Disease Study Group. *Ann Intern Med* 1997; 127: 1072–1079.
22 Friedman M, Serby CW, Menjoge SS, *et al.* Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. *Chest* 1999; 115: 635–641.
23 Burge PS, Calverley PM, Jones PW, *et al.* Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
24 Dewan NA, Rafique S, Kanwar B, *et al.* Acute exacerbation of COPD: factors associated with poor treatment outcome. *Chest* 2000; 117: 662–671.
25 Anthonisen NR, Wright EC, Hodgkin JE. Prognosis in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133: 14–20.
26 Parshall MB, Schwartzstein RM, Adams L, *et al.* An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med* 2012; 185: 435–452.
27 Schols AM, Slangen J, Volovics L, *et al.* Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1791–1797.
28 Landbo C, Prescott E, Lange P, *et al.* Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 1856–1861.
29 Mahler DA, Ward J, Waterman LA, *et al.* Patient-reported dyspnea in COPD reliability and association with stage of disease. *Chest* 2009; 136: 1473–1479.
30 Nishimura K, Izumi T, Tsukino M, *et al.* Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002; 121: 1434–1440.
31 Celli BR, Cote CG, Marin JM, *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005–1012.
32 Cote CG, Pinto-Plata VM, Marin JM, *et al.* The modified BODE index: validation with mortality in COPD. *Eur Respir J* 2008; 32: 1269–1274.
33 Soler-Cataluña JJ, Martínez-García MA, Sánchez LS, *et al.* Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. *Respir Med* 2009; 103: 692–699.
34 Marin JM, Alfageme I, Almagro P, *et al.* Multicomponent indices to predict survival in COPD: the COCOMICS study. *Eur Respir J* 2013; 42: 323–332.
35 Celli BR, Locantore N, Yates J, *et al.* Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 185: 1065–1072.
36 Puhan MA, Garcia-Aymerich J, Frey M, *et al.* Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 2009; 374: 704–711.
37 Jones RC, Donaldson GC, Chavannes NH, *et al.* Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE index. *Am J Respir Crit Care Med* 2009; 180: 1189–1195.
38 Divo M, Cote C, de Torres JP, *et al.* Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155–161.
39 Almagro P, Soriano JB, Cabrera FJ, *et al.* Short- and medium-term prognosis in patients hospitalized for COPD exacerbation: the CODEX index. *Chest* 2014; 145: 972–980.
40 Agustí A, Barberà JA, Wouters EFM, *et al.* Lungs, bone marrow, and adipose tissue. A network approach to the pathobiology of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 188: 1396–1406.
41 Donaldson GC, Seemungal TAR, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.
42 Vestbo J, Edwards LD, Scanlon PD, *et al.* Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011; 365: 1184–1192.
43 Freimer N, Sabatti C. The human phenome project. *Nat Genet* 2003; 34: 15–21.
44 Han MK, Agusti A, Calverley PM, *et al.* Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med* 2010; 182: 598–604.
45 Drazen JM, Fabbri LM. Ageing and multimorbidity. *Eur Respir J* 2014; 44: 557.
46 Faner R, Cruz T, López-Giraldo A, *et al.* Network medicine, multimorbidity and the lung in the elderly. *Eur Respir J* 2014; 44: 775–788.
47 Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. *Eur Respir J* 2014; 44: 1055–1068.
48 Patel AR, Donaldson GC, Mackay AJ, *et al.* The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD. *Chest* 2012; 141: 851–857.
49 Mannino DM, Thorn D, Swensen A, *et al.* Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32: 962–969.
50 de Torres JP, Marín JM, Casanova C, *et al.* Lung cancer in patients with chronic obstructive pulmonary disease – incidence and predicting factors. *Am J Respir Crit Care Med* 2011; 184: 913–919.
51 Wilson DO, Leader JK, Fuhrman CR, *et al.* Quantitative computed tomography analysis, airflow obstruction, and lung cancer in the Pittsburgh lung screening study. *J Thorac Oncol* 2011; 6: 1200–1205.
52 Vanfleteren LE, Spruit MA, Groenen M, *et al.* Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187: 728–735.

53 Donaldson GC, Hurst JR, Smith CJ, *et al.* Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097.
54 Bowler RP, Kim V, Regan E, *et al.* Prediction of acute respiratory disease in current and former smokers with and without COPD. *Chest* 2014; 146: 941–950.
55 Tan WC, Bourbeau J, Hernandez P, *et al.* Exacerbation-like respiratory symptoms in individuals without chronic obstructive pulmonary disease: results from a population-based study. *Thorax* 2014; 69: 709–717.
56 Marin JM, Soriano JB, Carrizo SJ, *et al.* Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. *Am J Respir Crit Care Med* 2010; 182: 325–331.
57 Jha P, Peto R. Global effects of smoking, of quitting, and of taxing tobacco. *N Engl J Med* 2014; 370: 60–68.
58 Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. *Am J Respir Crit Care Med* 2002; 166: 675–679.
59 Parkes G, Greenhalgh T, Griffin M, *et al.* Effect on smoking quit rate of telling patients their lung age: the Step2quit randomised controlled trial. *BMJ* 2008; 336: 598–600.
60 Bednarek M, Gorecka D, Wielgomas J, *et al.* Smokers with airway obstruction are more likely to quit smoking. *Thorax* 2006; 61: 869–873.
61 Stratelis G, Mölstad S, Jakobsson P, *et al.* The impact of repeated spirometry and smoking cessation advice on smokers with mild COPD. *Scand J Prim Health Care* 2006; 24: 133–139.
62 Kotz D, Wesseling G, Huibers MJH, *et al.* Efficacy of confronting smokers with airflow limitation for smoking cessation. *Eur Respir J* 2009; 33: 754–762.
63 Tashkin D, Kanner R, Bailey W, *et al.* Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* 2001; 357: 1571–1575.
64 Tashkin DP, Rennard S, Hays JT, *et al.* Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. *Chest* 2011; 139: 591–599.
65 Tønnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. *Chest* 2006; 130: 334–342.
66 Wagena EJ, van der Meer RM, Ostelo RJ, *et al.* The efficacy of smoking cessation strategies in people with chronic obstructive pulmonary disease: results from a systematic review. *Respir Med* 2004; 98: 805–815.
67 Wilson I. Depression in the patient with COPD. *Int J Chron Obstruct Pulmon Dis* 2006; 1: 61–64.
68 Rigotti NA, Pipe AL, Benowitz NL, *et al.* Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. *Circulation* 2010; 121: 221–229.
69 Ellerbeck EF, Mahnken JD, Cupertino AP, *et al.* Effect of varying levels of disease management on smoking cessation: a randomized trial. *Ann Intern Med* 2009; 150: 437–446.
70 Fiore MC, Jaen CR, Baker TB, *et al.* Treating tobacco use and dependence: 2008 update. Clinical Practice Guidelines. Rockville, U.S., Department of Health and Human Services, 2008.
71 Crowley TJ, Macdonald MJ, Walter MI. Behavioral anti-smoking trial in chronic obstructive pulmonary disease patients. *Psychopharmacology (Berl)* 1995; 119: 193–204.
72 Etter J-F, Bullen C, Flouris AD, *et al.* Electronic nicotine delivery systems: a research agenda. *Tob Control* 2011; 20: 243–248.
73 Etter J-F, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* 2011; 106: 2017–2028.
74 Goniewicz MK, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: an internet survey. *Drug Alcohol Rev* 2013; 32: 133–140.
75 Bertholon JF, Becquemin MH, Annesi-Maesano I, *et al.* Electronic cigarettes: a short review. *Respiration* 2013; 86: 433–438.
76 Schraufnagel DE, Blasi F, Drummond MB, *et al.* Electronic cigarettes. A position statement of the forum of international respiratory societies. *Am J Respir Crit Care Med* 2014; 190: 611–618.
77 Buist AS, Sexton GJ, Nagy JM, *et al.* The effect of smoking cessation and modification on lung function. *Am Rev Respir Dis* 1976; 114: 115–122.
78 Jiménez-Ruiz C, Solano S, Viteri SA, *et al.* Harm reduction – a treatment approach for resistant smokers with tobacco-related symptoms. *Respiration* 2002; 69: 452–455.
79 Rennard SI, Daughton D, Fujita J, *et al.* Short-term smoking reduction is associated with reduction in measures of lower respiratory tract inflammation in heavy smokers. *Eur Respir J* 1990; 3: 752–759.
80 Simmons MS, Connett JE, Nides MA, *et al.* Smoking reduction and the rate of decline in FEV1: results from the Lung Health Study. *Eur Respir J* 2005; 25: 1011–1017.
81 Hughes JR, Carpenter MJ. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine Tob Res* 2006; 8: 739–749.
82 Tetrault JM, Crothers K, Moore BA, *et al.* Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. *Arch Intern Med* 2007; 167: 221–228.
83 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
84 Tashkin DP, Celli B, Senn S, *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.
85 Jenkins CR, Jones PW, Calverley PM, *et al.* Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respir Res* 2009; 10: 59.
86 Burgel PR, Paillasseur JL, Dusser D, *et al.* Tiotropium might improve survival in subjects with COPD at high risk of mortality. *Respir Res* 2014; 15: 64.
87 Celli BR, Thomas NE, Anderson JA, *et al.* Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008; 178: 332–338.
88 Decramer M, Celli B, Kesten S, *et al.* Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009; 374: 1171–1178.
89 Chong J, Karner C, Poole P. Tiotropium *versus* long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 9: CD009157.

90 Rabe KF, Fabbri LM, Israel E, *et al.* Effect of ADRB2 polymorphism on the efficacy of salmeterol and tiotropium in preventing COPD exacerbations: a prespecified substudy of the POET-COPD trial. *Lancet Respir Med* 2014; 2: 44–53.
91 Decramer ML, Chapman KR, Dahl R, *et al.* Once-daily indacaterol *versus* tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respir Med* 2013; 1: 524–533.
92 Calverley PM, Stockley RA, Seemungal TA, *et al.* Reported pneumonia in patients with COPD: findings from the INSPIRE study. *Chest* 2011; 139: 505–512.
93 Crim C, Calverley PM, Anderson JA, *et al.* Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J* 2009; 34: 641–647.
94 Wedzicha JA, Calverley PM, Seemungal TA, *et al.* The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008; 177: 19–26.
95 Aaron SD, Vandemheen KL, Fergusson D, *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; 146: 545–555.
96 Wedzicha JA, Decramer M, Ficker JH, *et al.* Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013; 1: 199–209.
97 Magnussen H, Disse B, Rodriguez-Roisin R, *et al.* Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014; 371: 1285–1294.
98 Price LC, Lowe D, Hosker HS, *et al.* UK National COPD Audit 2003: impact of hospital resources and organisation of care on patient outcome following admission for acute COPD exacerbation. *Thorax* 2006; 61: 837–842.
99 Rutten FH, Zuithoff NP, Hak E, *et al.* Beta-blockers may reduce mortality and risk of exacerbations in patients with chronic obstructive pulmonary disease. *Arch Intern Med* 2010; 170: 880–887.
100 Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. *Chest* 2011; 139: 165–173.
101 Spruit MA, Singh SJ, Garvey C, *et al.* An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; 188: e13–e64.
102 Vieira DS, Maltais F, Bourbeau J. Home-based pulmonary rehabilitation in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med* 2010; 16: 134–143.
103 Maltais F, Bourbeau J, Shapiro S, *et al.* Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2008; 149: 869–878.
104 van Wetering CR, Hoogendoorn M, Mol SJ, *et al.* Short- and long-term efficacy of a community-based COPD management programme in less advanced COPD: a randomised controlled trial. *Thorax* 2010; 65: 7–13.
105 van Wetering CR, Hoogendoorn M, Broekhuizen R, *et al.* Efficacy and costs of nutritional rehabilitation in muscle-wasted patients with chronic obstructive pulmonary disease in a community-based setting: a prespecified subgroup analysis of the INTERCOM trial. *J Am Med Dir Assoc* 2010; 11: 179–187.
106 Puhan MA, Gimeno-Santos E, Scharplatz M, *et al.* Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2011; 10: CD005305.
107 Casaburi R, Kukafka D, Cooper CB, *et al.* Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest* 2005; 127: 809–817.
108 Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1981; 1: 681–686.
109 Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* 1980; 93: 391–398.
110 Górecka D, Gorzelak K, Sliwiński P, *et al.* Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997; 52: 674–679.
111 Brochard L, Mancebo J, Wysocki M, *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333: 817–822.
112 Bott J, Carroll MP, Conway JH, *et al.* Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993; 341: 1555–1557.
113 Kramer N, Meyer TJ, Meharg J, *et al.* Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995; 151: 1799–1806.
114 Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000; 355: 1931–1935.
115 Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet* 2009; 374: 250–259.
116 Bhatt SP, Peterson MW, Wilson JS, *et al.* Noninvasive positive pressure ventilation in subjects with stable COPD: a randomized trial. *Int J Chron Obstruct Pulmon Dis* 2013; 8: 581–589.
117 Lamia B, Cuvelier A, Benichou J, *et al.* Bénéfices de la ventilation non invasive a domicile au décours d'une insuffisance respiratoire aigue hypercapnique chez les patients BPCO. Etude contrôlée randomisée multicentrique. Etude Non Invasive Ventilation in Obstructive Lung Disease (Nivold) [A multi-centre randomized controlled trial of domiciliary non-invasive ventilation vs long-term oxygen therapy in survivors of acute hypercapnic respiratory failure due to COPD. Non-invasive ventilation in obstructive lung disease (NIVOLD) study]. *Rev Mal Respir* 2012; 29: 1141–1148.
118 Clini E, Sturani C, Rossi A, *et al.* The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002; 20: 529–538.
119 Struik FM, Sprooten RT, Kerstjen HA, *et al.* Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomized, controlled, parallel-group study. *Thorax* 2014; 69: 826–834.
120 Struik FM, Lacasse Y, Goldstein RS, *et al.* Nocturnal noninvasive positive pressure ventilation in stable COPD: a systematic review and individual patient data meta-analysis. *Respir Med* 2014; 108: 329–337.
121 Kohnlein T, Windisch W, Kohler D, *et al.* Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med* 2014; 2: 698–705.